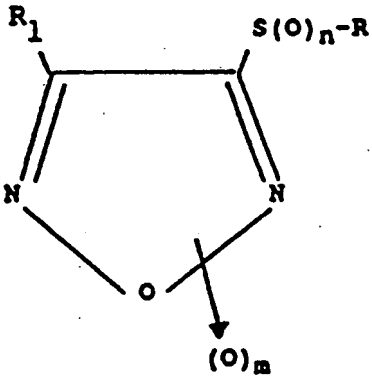




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/EP93/01559 (22) International Filing Date: 18 June 1993 (18.06.93) (30) Priority data: M192A001629 3 July 1992 (03.07.92) IT (71) Applicant (for all designated States except US): CHIESI FARMACEUTICI S.P.A. [IT/IT]; Via Palermo, 26/A, I-43100 Parma (IT). (72) Inventors; and (75) Inventors/Applicants (for US only) : CHIESI, Paolo [IT/IT]; BONGRANI, Stefano [IT/IT]; CIVELLI, Maurizio [IT/IT]; FOLCO, Giancarlo [IT/IT]; Via Palermo, 26/A, I-43100 Parma (IT). (74) Agent: MINOJA, Fabrizio; Studio Consulenza Brevettuale, Via Rossini, 8, I-20122 Milano (IT).		(81) Designated States: AU, BB, BG, BR, CA, CZ, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: PHARMACEUTICAL COMPOSITIONS HAVING ANTIAGGREGANT AND VASODILATING ACTIVITIES <div style="text-align: center;">  </div> <div style="text-align: right; margin-top: 10px;"> (I) </div>		
(57) Abstract Furoxan and furazan derivatives of formula (I) wherein R ₁ , R and m have the meanings defined in the specification, are useful as cardiovascular agents.		

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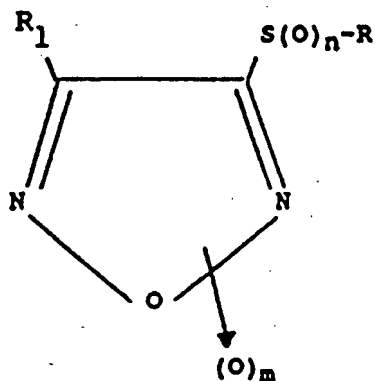
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"PHARMACEUTICAL COMPOSITIONS HAVING ANTIAGGREGANT AND VASODILATING ACTIVITIES"

The present invention refers to pharmaceutical compositions having antiaggregant and vasodilating activities, containing as the active principle one or more furoxan or furazan derivatives of formula I

5



(I)

10

wherein R_1 is $\text{C}_1\text{-C}_4$ -alkyl; $\text{C}_1\text{-C}_4$ -alkoxy; phenyl; an $\text{S(O)}_n\text{R}_2$ group wherein R_2 is $\text{C}_1\text{-C}_4$ alkyl or phenyl optionally substituted by $\text{C}_1\text{-C}_4$ -alkyl, or by halogen atoms;

15

R is $\text{C}_1\text{-C}_4$ -alkyl or phenyl optionally substituted by $\text{C}_1\text{-C}_4$ -alkyl or by halogen atoms;

$n = 0, 1$ or 2 ; $m = 0$ or 1 .

20

Compounds of formula I have been prepared and tested as antibacterial, antiprotozoal and antimycotic agents in Eur. J. Med. Chem. 12(2) 157-159, 1977 and in Eur. J. Med. Chem. 15(5) 485-487, 1980 in view of the fact that nitro and sulphonyl groups often impart anti-

25

microbial properties to a molecule.

Other authors described their synthesis without recognizing any biological activity (Farrar WV, J. Chem. Soc. 1964, 904-6; Gasco et al, J. Heterocycl.

Chem. 1973, 10, 587-90; Engbersen JFJ & Engberts JBFN, Syn. Commun. 1971, 1(2), 121-4; Jagt JC et al, Syn. Commun. 1974, 4(5), 311-16; Kelley JL et al, J. Heterocycl. Chem. 1977, 14(8), 1415-6).

5 Notwithstanding that "in vitro" antiaggregant activity has already been described for one of the compounds of formula I, namely 4-methyl-3-phenyl-sulfonylfuroxan (Biochemical Pharmacology 1992, 43(6), 1281-1288), no pharmacodynamics effects have been up to
10 now observed for the compounds of formula I so as to conceive their possible clinical use.

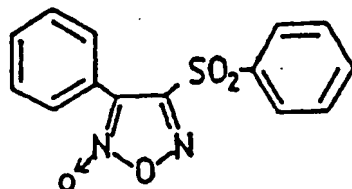
 It has now been found that furoxan and furazan derivatives of formula I have a remarkable vasodilating activity and, therefore, they may be conveniently used
15 as cardiovascular drugs, particularly as vasodilator, antihypertensive, antianginal, cerebral and coronary vasodilating and antithrombotic agents.

 Preferred compounds I are those wherein R_1 , is C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, phenyl or phenylsulphonyl
20 and, R is phenyl.

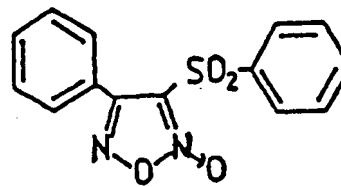
 The value of m is preferably 1.

 The preparation of the compounds I has been disclosed in J. med. Chem. 1992, 35, p 3296, starting from easily available anti-1-chloro-2-methyl-glyossime
25 which are reacted with suitable thiols in ether solution and in the presence of triethylamine to give the corresponding 1-arylthio-2-methylglyossime which are in turn oxidized by N_2O_4 yielding a furoxan mixture which can be separated into the single isomers or it can be
30 reduced by trimethylphosphite to give the corresponding furazans.

The preparation of the compounds 3-phenyl-4-phenylsulphonyl-furoxan (S77A) and 4-phenyl-3-phenylsulphonyl furoxan (S77B), having the following formulas



S77A



S77B

is disclosed in Eur. J. Med. Chem. 1980, 15(5), 485-487.

The pharmacological properties of the compounds I are hereinafter reported.

Methods

Platelet antiaggregant activity

Human blood from healthy volunteers who had not taken any drug during the past 2 weeks was collected in 1/10 volume of 3.8% trisodium citrate in plastic tubes. PRP (pH 7.6) was prepared by centrifugation at room temperature for 18 min at 160 g. Platelet poor plasma was prepared by subsequent centrifugation at 2000 g. Aggregation studies in PRP were performed according to the light transmission method of Born in a dual channel aggregometer (Elvi 840, Elvi Logos, Milan, Italy).

The tested compound dissolved in dimethyl sulfoxide (DMSO) or the vehicle alone was added to PRP 1 min. prior to addition of one of the following aggregating agents: collagen, ADP and PAF.

For each PRP the employed concentration of the aggregating agent was corresponding to the minimal con-

centration producing the maximal aggregating response in 5 minutes.

Such concentration was defined as "threshold aggregating concentration".

5 The induced aggregation was irreversible and was characterized by at least the 70-80% decrease in optical density.

An IC_{50} value was generated from regression analysis of the dose-response curve.

10 Vasodilating activity

Transverse rings were obtained from the descending thoracic aorta of male New-Zealand white rabbits. Four rings were joined together with surgical silk (2.0) to form a chain and placed in a 10 ml glass organ bath containing Krebs' Henseleit bicarbonate solution at 15 37°C, aerated with a mixture of 95% O_2 /5% CO_2 . Basal tension (2 g) was applied, followed by an equilibration period of 1 hour and the changes in isometric contraction were monitored with a force transducer (Basile, 20 mod. 7004) connected to a "Gemini 7070" Basile pen recorder.

Responses to various vasodilator agents were studied following enhancement of vascular tone with a sub-maximal concentration of Norepinephrine (NE, 1 μM) added 25 in the presence of 35 μM ascorbic acid.

Acetylcholine (Ach, 1 μM) was tested during the contraction evoked by NE, the bath rinsed and approx. 15 min. later the tone was again increased with NE. Glycerine trinitrate (NTG, 1.3 μM) was then added and 30 left in contact with the aortic rings in order to allow full development of its vasodilation. After extensive

rinsing of the preparations, a third NE-induced contraction was evoked; different drugs under investigation were then added in a cumulative fashion starting from 10 nM. Since all compounds investigated were dissolved in dimethyl sulfoxide (DMSO), a volume of DMSO equivalent to the total amount added with the drugs, was tested as control; the final concentration of DMSO in the organ bath did never exceed 0,05%, v/v. After attainment of maximal vasodilation, the aortic rings were extensively washed and another NE-induced contraction evoked, in order to verify full reversibility of the vasodilation. Ach and NTG were tested again in order to assess that the sensitivity of the preparations had remained constant.

The composition (mM) of the Krebs' buffer was: NaCl 118.9, KCl 4.66, KH_2PO_4 1.18, MgSO_4 1.1, CaCl_2 2.52, Glucosio 5.55, NaHCO_3 25 (Merck; Darmstadt, Germany); pH was 7.4. The following drugs were used: acetylcholine HCl (Sigma Chemical Company; St. Louis, Missouri, USA), glycerine trinitrate (Trinitrina^(R); Carlo Erba; Milan, Italy), dimethyl sulfoxide (Sigma), norepinephrine (Sigma), ascorbic acid (Merck).

Drug solutions were prepared on the day of the experiment, stored on ice, and added to the tissue bath in a volume not exceeding 50 μl . Norepinephrine and ascorbic acid were added to the Krebs' reservoir. Acetylcholine was added tot the tissue bath in a volume of 25 μl , from a solution 0.4 mM. Glycerine trinitrate was added to the tissue bath, in a volume of 50 μl , from a solution 60 $\mu\text{g/ml}$, obtained grinding a pill of Trinitrina^(R) in a potter containing 5 ml of distilla-

ted water.

Individual dose-response curves were linearized by plotting on semilog paper after probit transformation. The percentage of dilation was calculated, and the data from each tissue preparation were used for the calculation of mean responses. EC_{50} values were obtained from regression lines fitted with log curves by the least square method.

Results

10 Platelet antiaggregant activity

Besides compounds S77A and S77B (respectively 3-phenyl-4-phenylsulfonyl-furoxan and 4-phenyl-3-phenylsulfonyl-furoxan), other two furoxan derivatives, already known from the literature but never tested for biological activities, have been tested for antiaggregant activity: respectively,

3,4-bis(phenylsulfonyl)furoxan (Kelley J.L. et al., in J. Heterocycl. Chem. 1977, 14, 1415, hereinafter named SN010) and 4-ethoxy-3-phenylsulfonylfuroxan (Favar W.V. in J. Chem. Soc. 1964, part I, pp. 904-906, hereinafter named SN011).

The activity of the compounds under examination was compared with that of a known nitrovasodilator, sodium nitroprusside (NaNP).

25 The results expressed as IC_{50} are reported in Table 1.

4-phenyl-3-phenylsulfonylfuroxan, S77B, turned out to be particularly effective, being 5-10 times more potent than nitroprusside.

Table 1

Effect of S77A, S77B, 3,4-di(phenyl-sulfonyl)furoxan (SN010), 4-ethoxy-3-phenylsulfonylfuroxan (SN011) and NaNP on platelet aggregation in human PRP in vitro.

Results are expressed as the concentration required to inhibit by 50% the threshold aggregating concentration of various agents.

The data are expressed as mean value \pm S.E.M., n=5-8; NaNP n=2

Agent	S77A	S77B	SN010 IC ₅₀ \pm S.E.M. (μ M)	SN011	NaNP
Collagen	3.41 \pm 0.564	0.378 \pm 0.010	0.306 \pm 0.023	0.566 \pm 0.0626	1.95 \pm 0.115
PAF	0.845 \pm 0.0545	0.132 \pm 0.013	0.177 \pm 0.0077	0.158 \pm 0.0141	0.748 \pm 0.260
ADP	2.62 \pm 0.502	0.115 \pm 0.018	0.342 \pm 0.0574	0.386 \pm 0.0611	1.78 \pm 0.753

2) Vasodilating activity

The chemical structures of the tested compounds are reported in Table 2. The results of the vasodilating activity of the compounds under investigation are expressed as EC_{50} values against a fixed concentration of norepinephrine (1 μ M). Their potency ranges between 0.027 and 247 μ M and the most active compounds, S77B (4-phenyl-3-phenylsulfonyl-furoxan), SNO10 (3,4-di(phenyl-sulfonyl)furoxan), SNO11 (4-ethoxy-3-phenyl-sulfonylfuroxan), are approximately 4, 16 and 48 times more active than NTG, respectively.

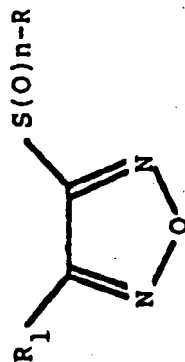
Furazans are endowed with a potency distinctly lower than that found for furoxans.

The class of phenyl-sulfonyl substituted furoxans, in particular, did show a marked vasodilating efficacy.

In a limited number of experiments the vasodilating effect of furazans and furoxans was tested in vascular preparations in which the endothelium had been completely removed through rubbing of the intima and verified by complete suppression of acetylcholine induced relaxation. The vasodilating capacity of the furazans and furoxans was fully independent of endothelial integrity.

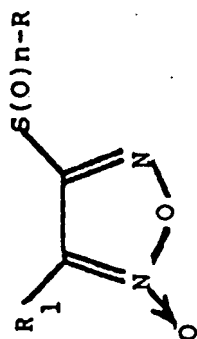
In the same animal model the vasodilating effect of the compound S77B had been confirmed also against KCl and an agonist of thromboxane A_2 , the compound U46619, with an EC_{50} value of 9.7×10^{-8} and 3.0×10^{-7} M respectively, so demonstrating that this new class of vasodilators can effectively inhibit the contraction induced by different contracturants.

Table 2: Results of the vasodilating activity of the compounds under investigation expressed as EC₅₀, against norepinephrine 1 µM.
Reference Compound: glyceryl trinitrate (UTG)



Compound	n	R	R ₁	EC ₅₀ values ± SE (µM)	Relative potency	9
NTG	-	-	-	1.3	1	
F43	1	C ₆ H ₅	CH ₃	inactive	-	
F102	2	C ₆ H ₅	CH ₃	inactive	-	
F42	2	C ₆ H ₅	CH ₃	65.2±4.16	0.019	
F41	2	p-CH ₃ C ₆ H ₄	CH ₃	51.1±3.83	0.025	
SNO7	2	p-CH ₃ OC ₆ H ₄	CH ₃	4.40±0.49	0.295	
SNO5	2	p-FC ₆ H ₄	CH ₃	247±147	0.005	
F55	2	p-ClC ₆ H ₄	CH ₃	inactive	-	
- continued -						

- continued -



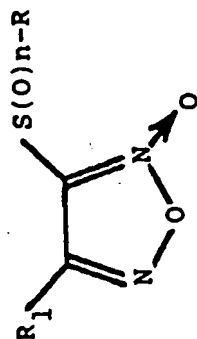
B

Compound	n	R	R ₁	EC ₅₀ values ± SE (μM)	Relative potency
S21A	0	C ₆ H ₅	CH ₃	inactive	-
S102A	1	C ₆ H ₅	CH ₃	12.6±0.76	0.103
S35A	2	C ₆ H ₅	CH ₃	5.00±0.12	0.260
S34A	2	p-CH ₃ C ₆ H ₄	CH ₃	7.06±0.21	0.184
SNO8	2	p-CH ₃ OC ₆ H ₄	CH ₃	3.21±0.22	0.405
SNO6(1)	2	p-FC ₆ H ₄	CH ₃	1.93±0.02	0.673
S55A	2	p-ClC ₆ H ₄	CH ₃	7.29±0.05	0.178
S77A	2	C ₆ H ₅	C ₆ H ₅	1.33±0.03	1

10

- continued -

- continued -



C

Compound	n	R	R ₁	EC ₅₀ values ± SE (μM)	Relative potency
S21B	0	C ₆ H ₅	CH ₃	14.9±0.29	0.087
S102B	1	C ₆ H ₅	CH ₃	27.8±0.59	0.047
S35B	2	C ₆ H ₅	CH ₃	2.32±0.08	0.560
S34B	2	p-CH ₃ C ₆ H ₄	CH ₃	2.12±0.14	0.613
SN09	2	p-CH ₃ OC ₆ H ₄	CH ₃	1.00±0.26	1.300

- continued -

- continued -

Compound	n	R	R ₁	EC ₅₀ values	Relative
SNO6 (2)	2	p-FC ₆ H ₄	CH ₃	2.86±0.07	0.454
S55B	2	P-ClC ₆ H ₄	CH ₃	4.59±0.05	0.283
S77B	2	C ₆ H ₅	C ₆ H ₅	0.33±0.15	3.96
SNO10	2	C ₆ H ₅	SO ₂ C ₆ H ₅	0.08±0.009	16.2
SNO11	2	C ₆ H ₅	OCH ₂ CH ₃	0.027±0.006	48.8

12

EC = Efficacy Concentration

SE = Standard Error

Relative potency = potency ratio in comparison with glyceryl trinitrate (NTG)

The present invention also relates to pharmaceutical compositions containing as the active principle the compounds of formula I or the salts thereof, in combination with pharmaceutically acceptable excipients, for use in cardiovascular therapy as vasodilators, antihypertensive, antianginal, cerebral and coronary vasodilators, antiaggregants and antithrombotics.

The daily dosage of the active principle can vary from 1 to 1,000 mg, preferably it will range from 5 to 500 mg.

The administration will be carried out through any routes, preferable by the oral or parenteral routes.

For the oral administration, the compounds can be formulated in solid or liquid formulations and they can be in form of capsules, tablets, sugar-coated pills, coated tablets, granules, powders, solutions, suspensions or emulsions.

The oral solid forms can contain conventional excipients, inert diluents, disgregation agents, binders and lubricants such as lactose, saccharose, sorbitol, mannitol; potato, cereal or maize starches, or amylopectin; cellulose and derivatives, gelatin, talc, magnesium or calcium stearate, polyvinylpyrrolidone, calcium phosphate, calcium carbonate, polyethylene glycol or silica.

The tablets can variously be coated according to well-known pharmaceutical procedures. Hard gelatin capsules can contain granulates of the active principle, together with solid, powdered excipients, such as lactose, saccharose, sorbitol, mannitol, starches (of the above indicated types), cellulose derivatives, gelatin,

and they can also contain stearic acid or magnesium stearate or talc.

Liquid formulations can be prepared by dissolving or dispersing the active principle in a pharmaceuti-
5 cally acceptable aqueous or non-aqueous solvent, which can also contain suspending agents, sweeteners, flavours or preservatives.

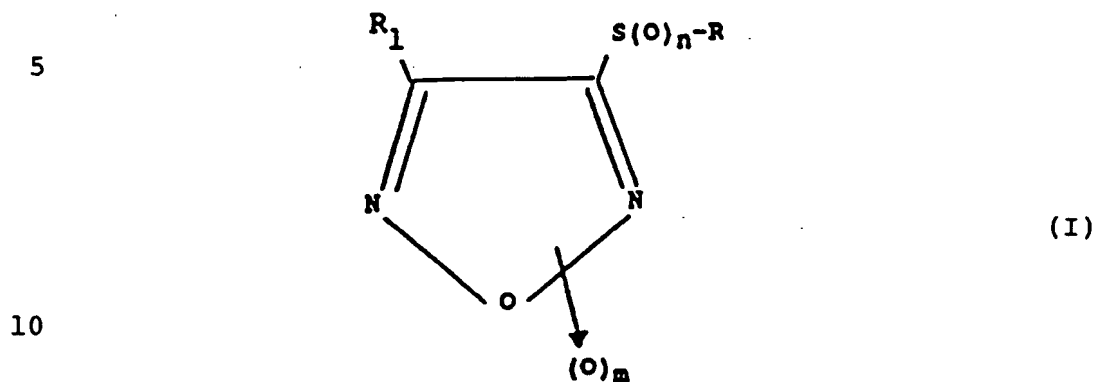
For injectable formulations for the parenteral administration, the excipients can be a pharmaceutically
10 acceptable sterile liquid such as water, saline solution, dextrose or fructose solutions, alcohol solutions, polyvinylpyrrolidone aqueous solutions optionally containing a stabilizing agent and/or a buffer, or oily carriers.

15 The active principle can either be dissolved in the liquid and sterilized before being distributed in vials, or it can suitably be freeze-dried, in which case vials containing injection liquid will be added to the package, to prepare the solution before use.

20 Another particularly advantageous method for the administration of the compounds of the invention are the transdermal systems, consisting of adhesive matrices which can be applied to the skin, in which the active principle is incorporated in a suitable concentration
25 and from which it is gradually released to the skin, to enter the blood stream.

CLAIMS

1. Compounds of formula I:



wherein R_1 is C_1 - C_4 -alkyl; C_1 - C_4 -alkoxy; phenyl; an $S(O)_nR_2$ group wherein R_2 is C_1 - C_4 alkyl or phenyl optionally substituted by C_1 - C_4 -alkyl, or by halogen atoms;

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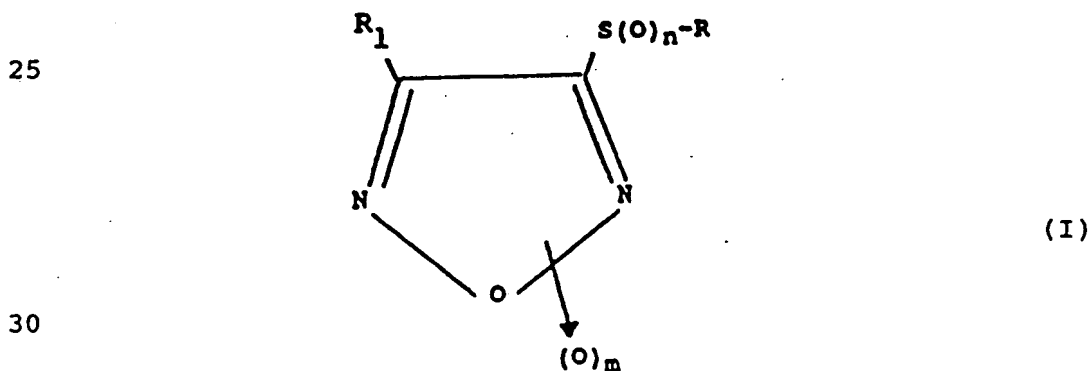
R is C_1 - C_4 -alkyl or phenyl optionally substituted by C_1 - C_4 -alkyl or by halogen atoms;

$n = 0, 1$ or 2 ; $m = 0$ or 1 , as cardiovascular agents.

2. Compounds of formula I as vasodilators, antihypertensives, antiangina agents, cerebral vasodilators, coronary vasodilators, antiaggregant, antithrombotic agents.

20

3. Compounds of formula I:



wherein R_1 is C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, phenyl or phenylsulphonyl and, R is phenyl of claims 1-3 as cardiovascular agents.

4. Compounds according to any claim wherein m is 1.
- 5 5. The use of compounds of formula I for the preparation of medicaments useful for the treatment of cardiovascular pathologies.
6. Pharmaceutical compositions containing as active principle a compound of formula I in admixture with a
10 suitable carrier.

INTERNATIONAL SEARCH REPORT

PCT/EP 93/01559

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC: Int.Cl. 5 C07D271/08; A61K31/41		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07D	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	IL FARMACO vol. 48, no. 2, May 1992, pages 321 - 334 R. CALVINO ET. AL 'Pharmacochemistry of the Furoxan Ring: Recent Developments. Presented at the 5th Meeting on Heterocyclic Structures in Medicinal Chemistry, Palermo May 17-20, 1992.' see the whole document ---	1-6
A	EP,A,0 038 438 (CASSELLA) 28 October 1981 see the whole document --- -/--	1-6
<p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search 20 OCTOBER 1993		Date of Mailing of this International Search Report - 3. 11. 93
International Searching Authority EUROPEAN PATENT OFFICE		Signature of Authorized Officer Bernd Kissler

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	<p>EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY.CHIMICA THERAPEUTICA vol. 12, no. 2, 1977, PARIS FR pages 157 - 159 CALVINO ET. AL. 'Furazan and Furoxan Sulfones: Synthesis and Antimicrobial activity.' cited in the application see compounds of tables I and III ---</p>	4
X	<p>EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY.CHIMICA THERAPEUTICA vol. 15, no. 5, 1980, PARIS FR pages 485 - 487 CALVINO ET. AL. 'Antimicrobial Properties of Some Furazan and Furoxan Derivatives.' cited in the application see examples in experimental section ---</p>	4
X	<p>JOURNAL OF THE CHEMICAL SOCIETY March 1964, LETCHWORTH GB pages 904 - 906 W. V. FARRAR 'The 3,4-Bisarenesulphonylfuroxans.' cited in the application compounds of formula I ---</p>	4
X	<p>J. HETEROCYCLIC CHEMISTRY vol. 10, 1973, pages 587 - 590 A. GASCO ET. AL. 'Unsymmetrically Substituted Furoxans. III. Methylnitrofuroxan: Its Structure and Behaviour Toward Nucleophilic Substitution.' cited in the application see examples 5 (a,b), 6 (a,b), 7(a,b), 8 (a,b) ---</p>	4
X	<p>SYNTHETIC COMMUNICATIONS vol. 1, no. 2, 1971, NEW YORK pages 121 - 124 J. B. F. N. ENGBERTS ET. AL. 'Reaction of Aliphatic Diazo Compounds with Dinitrogen Trioxide. A Facile Route to 3,4-Disubstituted 1,2,5-Oxadiazole-2-oxides (Furoxans).' cited in the application see examples in table ---</p>	4

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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	<p>SYNTHETIC COMMUNICATIONS vol. 4, no. 5, 1974, NEW YORK pages 311 - 316 A. M. VAN LEUSEN ET. AL. 'Synthesis of C-Sulfonylcarbohydroximoyl Chlorides from .alpha.Diazosulfones and Nitrosyl Chloride.' cited in the application compounds of formula 5</p> <p>---</p>	4
X	<p>J. HETEROCYCLIC CHEMISTRY vol. 14, 1977, pages 1415 - 1416 J. L. KELLEY ET. AL. 'Synthesis of Bis(Arylsulfonyl)furoxans from Aryl Nitromethyl Sulfones.' cited in the application see examples table II</p> <p>---</p>	4
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X	<p>JOURNAL OF MEDICINAL CHEMISTRY. vol. 35, no. 17, 1992, WASHINGTON US pages 3296 - 3300 A. GASCO ET. AL. '4-Methyl-3-(arylsulfonyl)furoxans: A new Class of Potent Inhibitors of Platelet Aggregation.' cited in the application see the whole document</p> <p>---</p>	1-6
X	<p>J. HETEROCYCLIC CHEMISTRY vol. 19, 1982, pages 427 - 430 R. CALVINO, R. FRUTTERO, A. GASCO, V. MORTARINI 'Unsymmetrically Substituted Furoxans.' see table 2</p> <p>---</p>	4

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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	JOURNAL OF THE CHEMICAL SOCIETY PERKIN TRANSACTIONS 2 1992, LETCHWORTH GB pages 1643 - 1646 R. CALVINO, A. GASCO, A. LEO 'An Analysis of the Lipophilicity of Furazan and Furoxan Derivatives Using the CLOGP Algorithm' see compounds 2j, 2k, 2l, 2m, 3j, 3k, 3m ---	4
A	ARZNEIMITTEL FORSCHUNG. DRUG RESEARCH vol. 42, no. 7, 1992, AULENDORF DE pages 921 - 925 A. M. GASCO ET. AL. 'Synthesis and Cardiovascular Properties of Furazanyl-1,4-dihydropyridines and of Furoxanyl Analogues.' see the whole document ---	1-6
X	TETRAHEDRON, (INCL. TETRAHEDRON REPORTS) vol. 41, no. 4, 1985, OXFORD GB pages 727 - 738 T. SHIMIZU ET. AL. 'Reaction of 3,4-Disubstituted 1,2,5-Oxadiazole-2-oxides with Dipolarophiles.' see furoxans in table 1 and 2 ---	4
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